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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

FEDOWITZ, MATTHEW L

ART UNIT	PAPER NUMBER
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1623

DATE MAILED: 04/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/814,399

Applicant(s)

QUAY ET AL.

Examiner

Matthew L. Fedowitz

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– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-40 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 1/10/2005.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ____.

DETAILED ACTION

Claims 1-40 are pending in this action.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 15, 16, 15-40 have been renumbered 15-42.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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A. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wenig (US 4,724,231), Grychowski et al. (US 6,745,760), Slot *et al.*, Garcia-Arieta *et al.* and Harris et al.

Claims 1-16 are drawn to a kit for the nasal drug delivery of a cyanocobalamin solution that comprises a container containing the cyanocobalamin solution and an actuator through which the cyanocobalamin is sprayed; where the spray pattern has an ellipticity ratio from about 1.0 to 1.4 at a height of 3 cm; where less than 5% of the emitted droplets are less than 10 μm in size; where the spray pattern has a major and minor axis of between 25 and 40 mm each; where the solution is comprised of citric acid at a concentration of 0.12% and sodium citrate at a concentration of 0.32% and has a pH of about 4-6; where the cyanocobalamin is in a concentration of about 0.5-1% by weight; where 50% of the droplets are 26.9 μm or less in size, 90% of the droplets are 55.3 μm or less in size and 10% of the droplets are 12.5 μm or less in size.

Grychowski et al. teach an intranasal device that can be characterized as a kit that contains a container and an actuator (see claims 1-65). Grychowski et al. does not teach an aqueous cyanocobalamin solution. Harris et al. teach that viscosity and particle size are particularly important in intranasal delivery systems (see abstract). The motivation to combine these to references comes from Harris et al. where it is stated viscosity, particle size and nasal clearance are important parameters in the design of nasal delivery systems. This motivation clearly demonstrates that one who is skilled in the art of nasal drug delivery systems would readily know what parameters to adjust to optimize a nasal formulation of cyanocobalamin. For example, one skilled in the art would readily be able to adjust the spray pattern ellipticity ratio, droplet size and spray pattern major and minor axes by selecting differing actuator tips as found in Grychowski et al. and adjusting the parameters as taught in Harris et al. As a result, these

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variables could be adjusted to provide the spray pattern ellipticity ratios, droplet sizes and spray pattern major and minor axes as claimed by the applicant for many formulations.

In regard to the cyanocobalamin formulation, Wenig teaches a pharmaceutical composition comprising cyanocobalamin and water with no mercury for intranasal administration (see Examples 1-3) with a viscosity that can be adjusted to below 1000 cPs (see column 3 lines 1-5 where Wenig states that the important point is to use an amount which will achieve the selected viscosity) and has a similar bioavailability to that of a gel formulation (see Applicant's specification pp. 17-18); where the solution contains citric acid and sodium citrate with a pH of about 5 (see column 2 lines 52-58 and example 3); where the composition contains humectants such as sorbitol, propylene glycol and glycerin with the glycerin present at a concentration of about 2.23% (see column 3 lines 10-13 and example 1A and 1C); where a preservative is present such as benzyl alcohol, chlorobutanol and benzalkonium chloride with the benzalkonium present at a concentration of about 0.02% (see lines 26-30 and example 1B) and where solution contains an optimized formulation with 0.5% cyanocobalamin present, 0.12% citric acid and 0.32% sodium citrate all present as a percent of total weight (see example 1C and 3) and where the optimized formulation containing the equivalents of cyanocobalamin, citric acid, sodium citrate, glycerin, benzalkonium chloride and water wherein said solution of cyanocobalamin is suitable for intranasal administration (see example 2).

Wenig does not teach a formulation that is in aqueous form; the exact concentration of humectants in the formulation, the exact concentration of preservatives present in the formulation or the exact concentration of a formulation that contains cyanocobalamin, citric acid,

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and sodium citrate. Wenig also does not teach the intranasal formulation in the same format as the applicant.

Garcia-Arieta *et al.* teach the nasal administration of cyanocobalamin in nasal solution (spray and drops) as well as the bioavailability of this formulation (see p. 1412 second column under nasal bioavailability studies p. 1415 figure 4 and table 2). Slot *et al.* also teaches an intranasal formulation of hydroxocobalamin preserved solution (see p. 431 first column under Study Design). The exact concentration of preservatives, humectants and cyanocobalamin are not taught by either of these references, however, one skilled in the art of pharmaceutical formulations would be able to optimize such formulations with the humectants, preservatives and cyanocobalamin to modulate the viscosity and pH to obtain a therapeutically useful formulation.

The motivation to combine these references is provided by Wenig where it is stated that the important point is to use an amount of thickening agent that will achieve the selected viscosity (see column 3 lines 7-8). By stating this in such manner, Wenig proposes that the viscosity can be changed to any desired viscosity by simply altering the amount of the thickening agent. Further, if the one skilled in the art were interested in forming a solution rather than a gel, the viscosity could be decreased in a manner as suggested by Wenig while maintaining the formulation with the humectants, preservatives and cyanocobalamin as found in the Wenig patent.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings above to obtain the kit as claimed in the instant application. All of the intranasal drug delivery devices and parameters for adjustment to optimize formulations as well as formulation ingredients, which are combined in the instant application,

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are taught in the art, and the nature of the formulation ingredients are correlative with the uses as found in the art. Obviousness based on similarity of formulation and function of those ingredients of the formulation entails motivation to make the claimed kit in expectation that compounds similar in formulation will have similar properties; therefore, one of ordinary skill in the art would be motivated to make the claimed compositions in searching for new formulations of cyanocobalamin.

B. Claims 20-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wenig (US 4,724,231), Grychowski et al. (US 6,745,760), Slot *et al.*, Garcia-Arieta *et al.* and Harris et al.

Claims 20-42 are drawn to a method for administering a cyanocobalamin solution comprised of infusing the nose with an aqueous solution of cyanocobalamin, wherein the solution of cyanocobalamin is administered with the kit as described above; where the solution contains specific concentrations of cyanocobalamin, citric acid, sodium citrate, glycerin and benzalkonium chloride that results in a bioavailability of at least about 7% relative to an intramuscular injection. And where the kit for the nasal drug delivery of a cyanocobalamin solution comprises a container containing the cyanocobalamin solution and an actuator through which the cyanocobalamin is sprayed; where the spray pattern has an ellipticity ratio from about 1.0 to 1.4 at a height of 3 cm; where less than 5% of the emitted droplets are less than 10 μm in size; where the spray pattern has a major and minor axis of between 25 and 40 mm each; where the solution is comprised of citric acid at a concentration of 0.12% and sodium citrate at a concentration of 0.32% and has a pH of about 4-6; where the cyanocobalamin is in a concentration of about 0.5-1% by weight; where 50% of the droplets are 26.9 μm or less in size,

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90% of the droplets are 55.3 μ m or less in size and 10% of the droplets are 12.5 μ m or less in size. Still further, the claims are drawn to a method of elevating the vitamin B-12 level in the cerebral spinal fluid using the parameters described above.

As relating to claims 20-42, the teachings from Wenig relating to the compositions from which the methods depend therefrom, are discussed above. Wenig also teaches a method of administering cyanocobalamin (see claims 17-27) that is specifically directed at nasal administration (see column 2 lines 16-23). Wenig does not teach the formulation in a solution form, however, Garcia-Arieta *et al.* and Slot *et al.* do teach such cyanocobalamin solutions, as discussed above. Further, Wenig does not teach the exact formulations for the cyanocobalamin formulations, however, as discussed above, one of ordinary skill in the art would know how to optimize such formulations in order to achieve the formations claimed.

Wenig provides the motivation to create such a solution by stating that the thickening agent may be added to achieve the viscosity desired as discussed above.

Still further, Grychowski *et al.* and Harris *et al.* teach intranasal drug delivery systems and parameters from which the methods claimed depend therefrom and are discussed above as well as the motivation to combine these references.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings above to obtain the methods as claimed in the instant application. All of the intranasal drug delivery devices, parameters for adjusting the spray pattern ellipticity ratios, droplet sizes and spray pattern major and minor axes as well as formulation ingredients, which are combined in the instant application, are taught in the art, and the nature of the formulation ingredients are correlative with the methods as found in the prior

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art. Obviousness based on similarity of formulation and function of those ingredients of the formulation entails motivation to claim methods in expectation that compounds similar in formulation will have similar properties (as stated in the applicant's specification pp. 17-18 and in the methods found in Wenig method claims 17-27); therefore, one of ordinary skill in the art would claim such methods for administering cyanocobalamin.

Claim Rejections - 35 USC § 112

A. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 14, 20, 31 and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The aforementioned claims are directed to a solution that, when administered intranasally, have a bioavailability of at least 7% relative to an intramuscular injection. An adequate representation regarding the bioavailability claimed would be one that provides all of the data necessary to calculate the bioavailability claimed relative to that of an intramuscular injection.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the factual considerations. In re Wands, 8 USPQ2d 1400 (CAFC). There are many factors to be considered when determining whether there is sufficient evidence

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to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include but are not limited to:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The level of one of ordinary skill;
5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The existence of working examples; and
8. The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Wands Analysis

1. The Breadth of the Claims.

The breadth of the instant claims are seen to encompass a composition that, when administered intranasally, has a bioavailability of at least 7% relative to an intramuscular injection; where the composition is a pharmaceutical aqueous solution of cyanocobalamin comprised of cyanocobalamin and water with a viscosity of less than about 1000 cPs for intranasal administration; where the cyanocobalamin is at a concentration of about 0.5% of total weight of solution, citric acid at a concentration of about 0.12%, sodium citrate at a concentration of about 0.32%, glycerin at a concentration of about 2.23%, benzalkonium chloride at a concentration of about 0.02%.

Further, the claims are drawn to a method of administering such a composition intranasally, as described above, by infusing the nose with an aqueous solution of cyanocobalamin where the composition has a bioavailability of about 7% relative to and intramuscular injection of cyanocobalamin. Still further, the claims are drawn to a method for elevating the vitamin B12 levels in the cerebral spinal fluid (CSF) by administering a solution of cyanocobalamin so that the average ratio of vitamin B12 in the CSF to that in the blood serum is increased to at least about 1.1 by administering the composition as described above where the composition has a bioavailability of about 7% relative to and intramuscular injection of cyanocobalamin.

2. The Nature of the Invention.

The nature of the invention relates to cyanocobalamin compositions and methods of using the compositions based on the bioavailability of about 7% relative to and intramuscular injection of cyanocobalamin.

There are several methods of assessing bioavailability in humans and other animals. The selection of methods depends on the nature of the drug product and makes use of such parameters as time of peak plasma concentration (t_{\max}), peak plasma concentration (C_{\max}) and the area under the plasma-time curve (AUC).

Relative bioavailability may be measured by comparing the respective AUCs after oral and IV administration and is calculated using the following formula:

$$\text{Bioavailability} = [((\text{AUC})_{\text{intranasal}}/\text{dose}_{\text{intranasal}})/((\text{AUC})_{\text{im}}/\text{dose}_{\text{im}})].$$

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3. The State of the Prior Art.

The applicant discloses several examples in the specification to demonstrate the relative bioavailability relating to the compositions and methods claimed. As stated above, in order to demonstrate relative bioavailability the applicant must provide four variables for the bioavailability equation $(AUC)_{\text{intranasal}}$, $\text{dose}_{\text{intranasal}}$, $(AUC)_{\text{im}}$ and dose_{im} . In example 1, the applicant discloses the intranasal dose ($\text{dose}_{\text{intranasal}}$) and the intramuscular dose (dose_{im}) (specification p. 14 second paragraph) and the AUC for the spray and gel intranasal doses but does not disclose the AUC for the intramuscular dose. In example 2, the applicant discloses the intranasal dose ($\text{dose}_{\text{intranasal}}$) and the intramuscular dose (dose_{im}) (specification p. 18 second paragraph under Example 2) but does not disclose any AUC data for either route of administration. As a result of this finding and the lack of adequate representations in the specification, the applicant has not enabled this aspect of the claimed composition or methods for using the same. The skilled artisan in this field would not accept the representations set forth in the instant disclosure as sufficient to enable cyanocobalamin compositions and methods of using the composition based on the bioavailability of about 7% relative to and intramuscular injection of cyanocobalamin.

4. The Level of Ordinary Skill

The level of skill is that of one with a doctoral understanding of pharmacokinetics and therapeutics. In addition, this understanding would encompass pharmaceutics and drug formulations.

5. The Level of Predictability in the Art

Pharmacokinetic profiles are predictable and are routinely demonstrated when an applicant claims that a formulation has a specific relative bioavailability. As such, it would be expected that the applicant could demonstrate that the formulations and methods claimed would have a bioavailability of cyanocobalamin, when administered nasally, of at least 7% relative to an intramuscular injection of cyanocobalamin. And in demonstrating this, the applicant would provide the data necessary to calculate the relative bioavailability.

6. The Amount of Direction Provided by the Inventor

The applicant has not demonstrated sufficient guidance provided in the form of adequate supporting representations or art recognized correlations in patent or non-patent literature. For example, the applicant discloses examples but does not provide the data necessary in those examples to show that the bioavailability of cyanocobalamin, when administered nasally, is at least 7% relative to an intramuscular injection of cyanocobalamin. Instead the applicant provides minimal administration data without providing sufficient AUC data and then states a conclusion that the applicant has shown a 7% relative bioavailability.

7. The Existence of Working Examples

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 27 USPQ2d 1510 (CAFC). The disclosure does not

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demonstrate sufficient evidence to support the applicant's claim to compositions and methods that the bioavailability of cyanocobalamin, when administered nasally, is at least 7% relative to an intramuscular injection of cyanocobalamin. Applicant's claims necessarily require disclosure or guidance in the art to accept the composition and methods claim to relative bioavailability commensurate in scope with the instant claims.

8. The Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure

In order to accomplish the showing that the bioavailability of cyanocobalamin, when administered nasally, is at least 7% relative to an intramuscular injection of cyanocobalamin, the applicant would have to state the AUC and doses administered for both the intranasal and intramuscular routes to calculate the bioavailability.

B. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 17, 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The aforementioned claims refer to the method of claim 12. Claim 12 is not a method claim and therefore it is unclear as to what the applicant is referring to.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew L. Fedowitz whose telephone number is (571) 272-

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3105. If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, James O. Wilson, can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Matthew L. Fedowitz, Pharm.D., J.D.
April 7, 2005

James O. Wilson
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